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TOXICOLOGY AND PATHOLOGY OF REPEATED DOSES OF MONOMETHYLHYDRAZINE IN MONKEYS

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AEROSPACE MEDICAL RESEARCH LABORATORIES
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FOREWORD

This study was performed in support of Project 6302, "Toxic Hazards of Propellants and Materials," Task 630202, "Pharmacology and Biochemistry," and Task 630201, "Toxicology." The work was performed from April 1964 to July 1964 in the Toxicology Branch, Toxic Hazards Division, Biomedical Laboratory. Valuable assistance rendered by Roman Patrick, Capt, USAF, MC, and David Harper, Capt, USAF, MC, of the Pathology Branch is gratefully acknowledged.

This technical report has been reviewed and is approved.

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ABSTRACT

The effects of daily repeated doses of monomethylhydrazine (MMH) were studied in monkeys. Groups of monkeys were given from 2.5 to 5 mg/kg MMH i.p. for a total of 23 doses. Other monkeys were given from 7 to 10 mg/kg MMH i.p. for up to 4 days. Baseline and weekly clinical laboratory measurements studied were complete blood count, serum glucose, alkaline phosphatase, and glutamic oxaloacetic transaminase. At the end of the exposures, necropsies were performed on all animals. Special studies included fat stains of fresh cryostat sections of heart, liver, and luxol fast blue stains of pons, cerebellum, basal ganglia, and insular cortex. Results of the experiments have delineated the limits of toxicity for MMH in primates, as evaluated by clinical chemistry, symptomatology, and pathological examination. Repeated doses of 5 mg/kg caused emesis and some convulsions when a total of 15 mg/kg was reached. Animals tolerated daily doses of 2.5 mg/kg for a total of 23 injections with no significant effects. Other animals tolerated 12 doses of 5 mg/kg per day after having received 5 mg/kg each day for 3 days and 2.5 mg/kg for 8 days or 95 mg/kg for a 4-week period. This experiment tends to negate a tolerance phenomenon. The most significant conclusions from the experiments are the relative lack of pathological (either anatomical or clinical) alterations seen in the acute intoxications and the extremely narrow limits between a no-effect and lethal dose level. Of extreme interest is the absence of kidney malfunction or renal pathology in these studies as contrasted by results seen in dogs at these dose levels. MMH causes marked renal damage in dogs.

SECTION I

EXPERIMENT I

EFFECTS OF SUBACUTE DOSES OF MONOMETHYLHYDRAZINE IN PRIMATES

INTRODUCTION

Increasing use of monomethylhydrazine (MMH) as a propellant has made mandatory the comprehensive study of its toxicity to protect personnel concerned with its use. As is customary in toxicological studies, the first experiments and determinations of LD_{50} were conducted in rats and mice (ref 1). Pharmacological investigations have been performed in cats and dogs (ref 1), and behavioral effects have been reported using trained primates (ref 2). In an effort to add more information to the overall toxicological picture, the present study involving repeated exposure of MMH to primates was undertaken.

MATERIALS AND METHODS

The monomethylhydrazine used in these experiments was obtained from Eastman Organic Chemicals and had a specific density of 0.8743. The liquid material as received was diluted with water to a concentration of 25 mg/ml immediately before injection. Volumes of diluted MMH injected i.p. were always less than 1 ml.

Twelve monkeys (Macaca mulatta), six males and six females, were used and ranged in weight from 3.18 to 4.31 kg. Two monkeys were used in a preliminary experiment to determine the dose of MMH that might be tolerated for daily injections over a 4-week period. Two monkeys, one male and one female, comprised a control group that received only saline injections for the entire period. The remaining eight monkeys were divided into two experimental groups, each receiving a dose regimen as shown in table I.

TABLE I

DOSAGE SCHEDULE

Group I	-	(4 monkeys; 2 M, 2 F)
		5 mg/kg - 3 days
		2.5 mg/kg - 20 days
Group II	-	(4 monkeys; 2 M, 2 F)
		5 mg/kg - 3 days
		2.5 mg/kg - 8 days
		5 mg/kg - 12 days
Controls	-	(2 monkeys; 1 M, 1 F)
		Saline - 23 days

In order to establish baseline values for the weekly clinical laboratory measurements, blood samples were drawn three times, two days apart, from each animal. A complete blood count (CBC), serum glucose, alkaline phosphatase, and glutamic oxaloacetic transaminase (SGOT) were determined for each blood sample, and averages and ranges were established for each animal before treatment with MMH or saline.

The monkeys were fasted overnight before the day on which blood samples were collected; otherwise they were allowed water ad libitum and fed standard monkey chow at the same time every day. The animals were maintained in individual cages. All animal holding facilities were air conditioned and the environment was maintained at constant temperature and humidity. No attempts were made to obtain urine or feces samples.

Blood samples were obtained from the femoral vein and placed either in heparinized glass tubes for hematology, or in tubes without anticoagulant and allowed to clot for 30 minutes before centrifugation. Serum was removed and clinical chemistry determinations were performed without delay.

Injections of MMH or saline were given intraperitoneally (i.p.) at the same time each morning, 5 days each week, for 4 weeks. Blood samples were drawn at weekly intervals on Wednesdays, and the monkeys were weighed each morning before injection. Clinical signs of illness, e.g., emesis, salivation, depression, convulsions, etc., were carefully noted and recorded.

At the end of the 4-week experimental period, the monkeys were necropsied. Tissues from selected organs were stained routinely with hematoxylin and eosin as well as with special Oil red O for detection of abnormal fat deposition. A complete histopathological evaluation was made of each MMH-treated and saline-injected animal.

RESULTS

Preliminary Establishment of Dose Level

Two monkeys were used for this study, one receiving daily doses of 5 mg/kg, the other receiving 10 mg/kg. On day 1, no symptoms were noted in either animal. On day 2, both animals displayed emesis at approximately 2 hours postinjection. On days 3, 4, and 5, the monkey on 5 mg/kg showed no further symptoms. On the other hand, the monkey receiving 10 mg/kg vomited and convulsed on day 3, convulsed on day 4, convulsed on day 5, and died later that same day.

As a result of these preliminary tests, we determined that the daily 5 mg/kg dose regimen appeared feasible for the 4-week study.

Clinical Symptomatology

On day 2 of the initial 5 mg/kg dose schedule, all eight test animals vomited. On day 3, four of eight vomited and two of eight convulsed. At this

point we decided to reduce the daily dose to 2.5 mg/kg. The group I animals were carried on the latter dose level for the remaining 20 injections and evinced only two instances of emesis for the entire period, one on day 19 and one on day 24. Occasional salivation was noted in group I, but no convulsions occurred.

On day 4, group II animals were also put on the 2.5 mg/kg daily dose schedule. During the ensuing 8 days of injections no emesis or convulsions were noted, and no signs of clinical illness were observed. On day 16, group II animals were again subjected to a 5.0 mg/kg dose regimen. All four animals vomited shortly after the injection on day 16. On day 18, three of four animals displayed emesis but no other symptoms. The only other instances of emesis in group II monkeys occurred on days 24 and 25 with one of four animals involved each time. Again, salivation was noted in some animals, but no convulsions occurred and by the end of day 31 (encompassing a total of 23 injection days), all animals appeared to be clinically well.

No clinical signs of illness or discomfort were noted in the saline control monkeys.

Weight Changes

There were no marked changes in weight over the 4-week experimental period as shown in table II and figure 1. Group II animals, however, tended to show an initial decrease in body weight at the end of the first week which remained fairly constant for the succeeding 3 weeks. On the basis of four animals only, this factor is difficult to evaluate properly.

Serum Glucose

Table III and figure 2 indicate that there were no significant differences in serum glucose between either group and control animals. No differences were noted between male and female monkeys. The apparent elevated glucose results obtained in week 3 are probably due to experimental laboratory conditions on the day of test, since the glucose determination is an enzymatic method and very temperature dependent. Since one of the control glucoses was elevated, that seems to obviate any other reasonable explanation.

The glucose results must be evaluated within the framework of this particular experimental protocol, that is, one sampling each week. Other workers (ref 3) have reported significant increases in blood glucose following hydrazine with peak levels at 2 hours and somewhat subnormal levels at 24 hours after a single exposure. Our results were obtained on animals bled only once a week.

TABLE II

EFFECTS OF MMH EXPOSURE ON WEIGHT (KG)

	Baseline	Week 1	Week 2	Week 3	Week 4
			Group I		
M	4.31	3.63	4.08	4.08	4.08
M	4.08	3.18	3.63	3.63	3.63
F	4.08	3.63	4.54	4.00	4.08
F	4.00	3.40	4.31	3.63	3.86
AV	4.12	3.46	4.14	3.84	3.91
			Group II		
M	4.08	3.18	3.40	3.40	3.50
M	3.63	3.08	3.40	2.95	3.00
F	3.18	2.72	2.72	2.80	2.72
F	3.18	2.72	2.72	2.27	2.40
AV	3.52	2.43	3.06	2.86	2.91
			Saline Controls		
M	3.63	3.40	3.63	3.63	3.63
F	3.40	3.00	4.08	3.18	3.40
AV	3.52	3.20	3.86	3.41	3.52

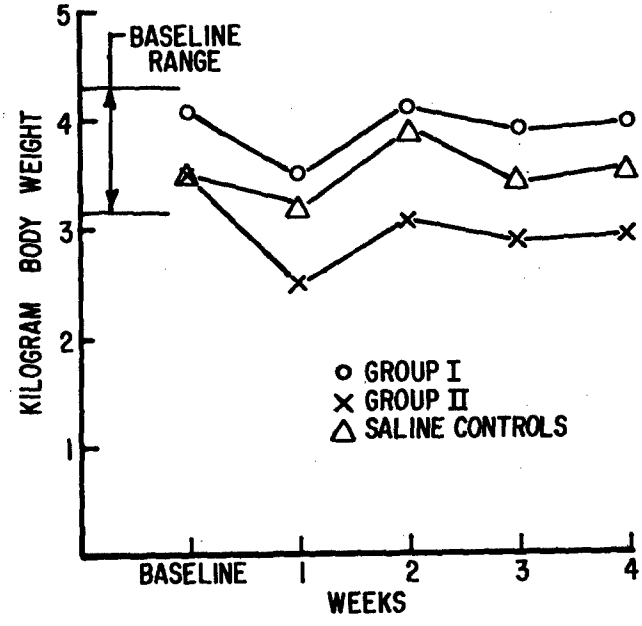

Figure 1. Effects of MMH on Weight in Monkeys

TABLE III

EFFECTS OF MMH ON SERUM GLUCOSE (MG/100 ML)

	Baseline	Week 1	Week 2	Week 3	Week 4
			Group I		
M	95	79	140	66	96
M	97	105	96	65	85
F	100	93	81	141	57
F	97	105	92	184	63
AV	97.3	95.5	102.3	114	75
			Group II		
M	98	93	92	141	61
M	117	107	100	221	58
F	103	93	111	160	81
F	95	105	122	85	63
AV	103.2	99.5	106.3	151.8	65.8
			Saline Controls		
M	110	113	107	80	63
F	89	90	111	193	63
AV	99.5	101.5	109	136.5	63

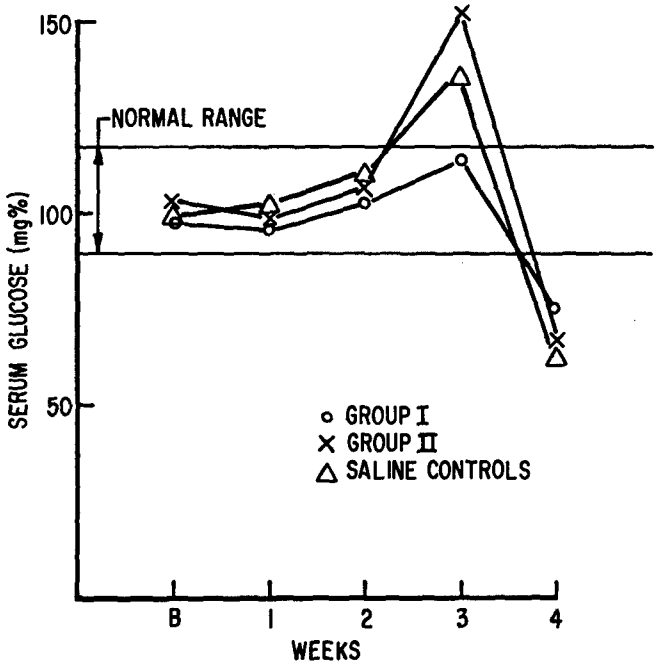

Figure 2. Effects of MMH on Serum Glucose in Monkeys

Serum Glutamic Oxaloacetic Transaminase

Table IV and figure 3 show that there are no significant differences between any experimental group and its control group. The elevated values obtained in all groups, including controls, at week 1 are probably due to environmental conditions in the chemistry laboratory on that day. Since values on succeeding weeks remain within the limits of all baselines, there was apparently no severe pathological damage to those organs which release this enzyme into the peripheral blood.

Serum Alkaline Phosphatase

Table V and figure 4 show no significant differences between treated animals and control animals. What appear to be real differences between males and females in the normal levels of serum alkaline phosphatase may be attributed to the small number of animals used in this experiment. Other long-range studies performed in this laboratory, involving several hundred monkeys, indicate that there are no statistical differences in serum alkaline phosphatase attributable to sex. Unfortunately, the ages of monkeys used in these experiments were not known. This single factor may account for the differences noted in our results, since it is known that in humans, children have higher blood levels than adults.

Pathological Evaluation

Complete necropsies were performed on eight monkeys receiving MMH and two monkeys receiving only saline. Special studies conducted included fat stains of fresh cryostat sections of heart, liver, and kidney; Oil red O stains of the same tissues from four animals and of liver from three animals; two sections of brain from each animal including pons, cerebellum, basal ganglia, and insular cortex (luxol fast blue stains were used to demonstrate the integrity of myelin sheaths); and studies of both smears and sections of femoral bone marrow.

Microscopic examination of tissue sections from these experimental animals indicated that no pathological alteration occurred following MMH dosage. All fat stains were negative. Alterations which were described in the liver also appeared in the control monkeys and could represent artifacts; in any event, they were not significant.

TABLE IV

EFFECTS OF MMH ON SGOT
(REITMAN-FRANKEL UNITS)

Baseline	Week 1	Week 2	Week 3	Week 4
		Group I		
M 27	28	30	14	19
M 30	30	22	38	18
F 28	80	13	14	10
F 17	70	14	10	16
AV 25.5	52	19.8	19	15.8
		Group II		
M 24	30	20	26	33
M 23	90	20	28	23
F 28	90	46	29	32
F 33	78	40	30	52
AV 27	72	31.5	28.3	35
		Saline Controls		
M 24	74	22	20	17
F 23	85	28	28	18
AV 23.5	79.5	26	24	17.5

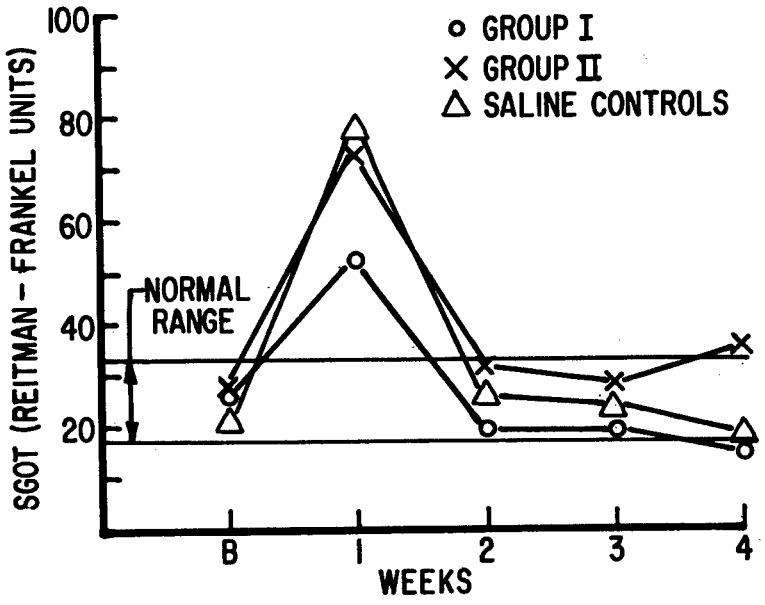

Figure 3. Effects of MMH on Serum Transaminase (SGOT)

TABLE V

EFFECTS OF MMH ON SERUM ALKALINE PHOSPHATASE
(KLEIN-BABSON-READ UNITS)

	Baseline	Week 1	Week 2	Week 3	Week 4
			Group I		
M	20	17	21	15	23
M	27	16	34	24	35
F	10	7	8	7	9
F	9	6	8	8	10
AV	16.5	11.5	17.8	13.5	19.3
			Group II		
M	19	14	15	15	21
M	19	17	26	18	21
F	10	6	8	7	8
F	9	6	5	4	6
AV	14.3	10.8	13.5	11	14
			Saline Controls		
M	16	20	28	18	32
F	15	12	19	11	21
AV	15.5	16	23.5	14.5	26.5

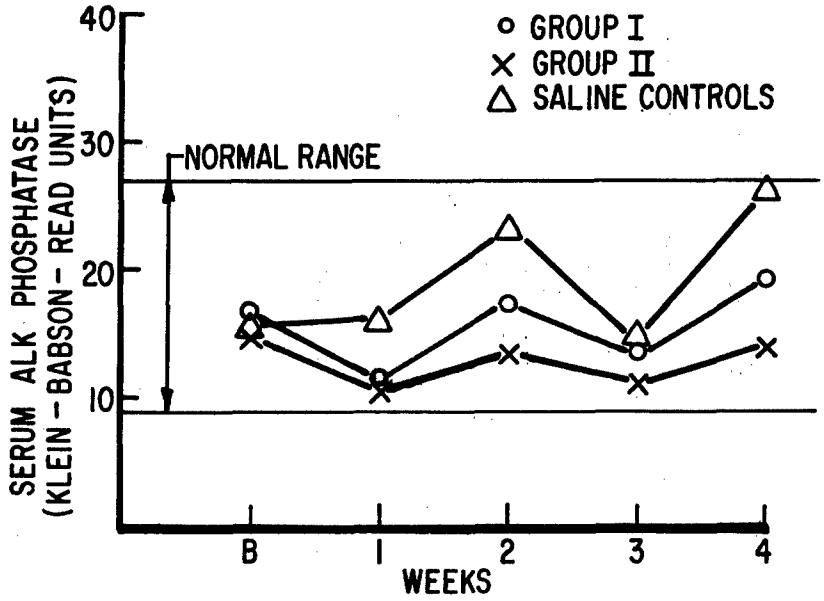

Figure 4. Effects of MMH on Serum Alkaline Phosphatase

SECTION II

EXPERIMENT II

PATHOLOGICAL EVALUATION OF ACUTE DOSES OF MONOMETHYLHYDRAZINE IN PRIMATES

INTRODUCTION

Since experiment I did not provide any demonstrable histopathological alterations in monkeys treated with daily doses of either 5 mg/kg or 2.5 mg/kg for a period of 4 weeks, a further investigation was performed which was specifically designed to produce clinical symptoms of illness and to provide material for pathological evaluation of organ damage incurred. Particular interest was directed toward the livers and kidneys of acutely exposed monkeys.

MATERIALS AND METHODS

The monomethylhydrazine (MMH) used in these experiments was prepared as described in experiment I.

Five male Macaque monkeys weighing from 2.40 to 5.91 kg were used. Two monkeys served as controls and received only saline injections. Three monkeys each received varying intraperitoneal (i.p.) doses of MMH on succeeding days until they succumbed and were necropsied. The exact doses for each animal are found in table VI.

TABLE VI

DOSAGE

Monkey No.	Day 1	Day 2	Day 3	Day 4	Comments
N-00	saline	saline	saline	saline	no symptoms
N-02	saline	saline	saline	saline	no symptoms
N-04	7 mg/kg	10 mg/kg	7 mg/kg	10 mg/kg	died on day 4
N-06	7 mg/kg	10 mg/kg	7 mg/kg	———	died on day 3
A-10	7 mg/kg	10 mg/kg	———	———	died on day 2

Blood samples were collected from each monkey for determinations of serum alkaline phosphatase and glutamic oxaloacetic transaminase. Two determinations were run on each animal to establish individual baseline levels before treatment with either MMH or saline, and blood was withdrawn for analysis each secondary day before MMH injection.

All animals were observed closely for clinical symptoms, and food intake of control monkeys was carefully matched to that of the MMH treated animals.

RESULTS

Symptomatology

No clinical symptoms of illness were noted in any of the 3 MMH treated animals receiving 7 mg/kg on day 1. When the dose was increased to 10 mg/kg on day 2, one animal convulsed three times (at 3.0, 5.5, and 5.75 hours) and one animal died after 3 hours.

On day 3 the dose was again reduced to 7 mg/kg for the remaining two animals, one of which convulsed at 3 hours following injection and was killed in a terminal comatose condition at 7 hours. On the fourth day of injection, only one monkey remained and it received 10 mg/kg. This animal convulsed first at 3 hours following injection, became comatose immediately thereafter and was killed in a terminal condition at 7 hours.

Serum Enzymes

The results shown in table VII are obviously without statistical significance and are reported without comment.

TABLE VII

SGOT

Monkey No.	Baseline	Day 2	Day 3	Day 4
N-00	31	34	33	19
N-02	35	38	52	44
N-04	23	26	20	170*
N-06	35	54	19	--
A-10	38	28	--	--

SERUM ALKALINE PHOSPHATASE

N-00	33	34	20	21
N-02	26	31	31	20
N-04	26	35	21	24*
N-06	27	35	27	--
A-10	32	37	--	--

*Terminal blood sample

Pathological Evaluation of Exposed Monkeys

Complete postmortem examinations were performed on three monkeys receiving MMH i.p. and on two monkeys that were used as controls, receiving saline injections only. Special studies included fat stains on heart,

kidney, and liver tissue of all animals. Brain and marrow tissue were stained with hematoxylin and eosin, routinely.

Significant differences found between the experimental and control groups were confined to the liver, where the experimental animals manifested moderate amounts of fatty infiltration with Oil red O stain. The control animals, with the same stain, showed only traces or minimal infiltration of fat in the liver. Vacuolization of liver cells varied from a trace to moderate amount in the experimental animals; this change was absent in both control animals.

Minimal fatty infiltration in the renal medulla was seen with Oil red O stain in one animal from both experimental and control groups. No fat was observed in the heart tissue of any monkey.

A complicating factor was seen in both animals from the control group. These animals showed histologic evidence of lung mite disease, as did two of the experimental animals.

One control animal showed foci of lymphocytes and histiocytes in the myocardium. One of the experimental animals showed tiny cerebellar hemorrhages, perivascular in origin. This animal had severe convulsions which may have accounted for this change.

SECTION III

DISCUSSION AND CONCLUSIONS

These experiments have apparently delineated the limits of toxicity for MMH in primates, as evaluated by clinical chemistry, overt symptomatology, and pathological examination. Single doses of up to 10 mg/kg MMH, by the i.p. route of administration, have produced no signs of illness, no changes in serum glucose, glutamic oxaloacetic transaminase, or in alkaline phosphatase. Repeated doses of 5 mg/kg appear to cause emesis and perhaps convulsions when a total dose of 15 mg/kg has been reached. All animals tolerated doses of 2.5 mg/kg per day for a total of 23 injections, representing a total dose of 65 mg/kg, with no demonstrable effects. Another group of monkeys appeared to tolerate 12 successive doses of 5 mg/kg per day after they had previously been subjected to three days of 5 mg/kg plus 8 days of 2.5 mg/kg. The latter dose regimen represented a total dose of 95 mg/kg per animal over the 4-week period. Speculation relative to a possible tolerance build-up phenomenon for MMH does not seem warranted at this time, although the possibility cannot be excluded on the basis of these data.

The most significant conclusions to be drawn from these two series of experiments in monkeys are the relative lack of pathological alterations seen even in acute intoxications, and the extremely narrow limits between a no-effect and lethal dose level. The complete absence of kidney malfunction or renal pathology in these studies is in direct contrast to other results seen in dogs at the same dose levels. The latter studies are currently in progress and will be reported at a later date.

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The effects of daily repeated doses of monomethylhydrazine (MMH) were studied in monkeys. Groups of monkeys were given from 2.5 to 5 mg/kg MMH i.p. for a total of 23 doses. Other monkeys were given from 7 to 10 mg/kg MMH i.p. for up to 4 days. Baseline and weekly clinical laboratory measurements studied were complete blood count, serum glucose, alkaline phosphatase, and glutamic oxaloacetic transaminase. At the end of the exposures, necropsies were performed on all animals. Special studies included fat stains of fresh cryostat sections of heart, liver, and luxol fast blue stains of pons, cerebellum, basal ganglia, and insular cortex. Results of the experiments have delineated the limits of toxicity for MMH in primates, as evaluated by clinical chemistry, symptomatology, and pathological examination. Repeated doses of 5 mg/kg caused emesis and some convulsions when a total of 15 mg/kg was reached. Animals tolerated daily doses of 2.5 mg/kg for a total of 23 injections with no significant effects. Other animals tolerated 12 doses of 5 mg/kg per day after having received 5 mg/kg each day for 3 days and 2.5 mg/kg for 8 days or 95 mg/kg for a 4-week period. This experiment tends to negate a tolerance phenomenon. The most significant conclusions from the experiments are the relative lack of pathological (either anatomical or clinical) alterations seen in the acute intoxications and the extremely narrow limits between a no-effect and lethal dose level. Of extreme interest is the absence of kidney malfunction or renal pathology in these studies as contrasted by results seen in dogs at these dose levels. MMH causes marked renal damage in dogs.

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It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as *(TS)*, *(S)*, *(C)*, or *(U)*.

There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. KEY WORDS: Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, rules, and weights is optional.